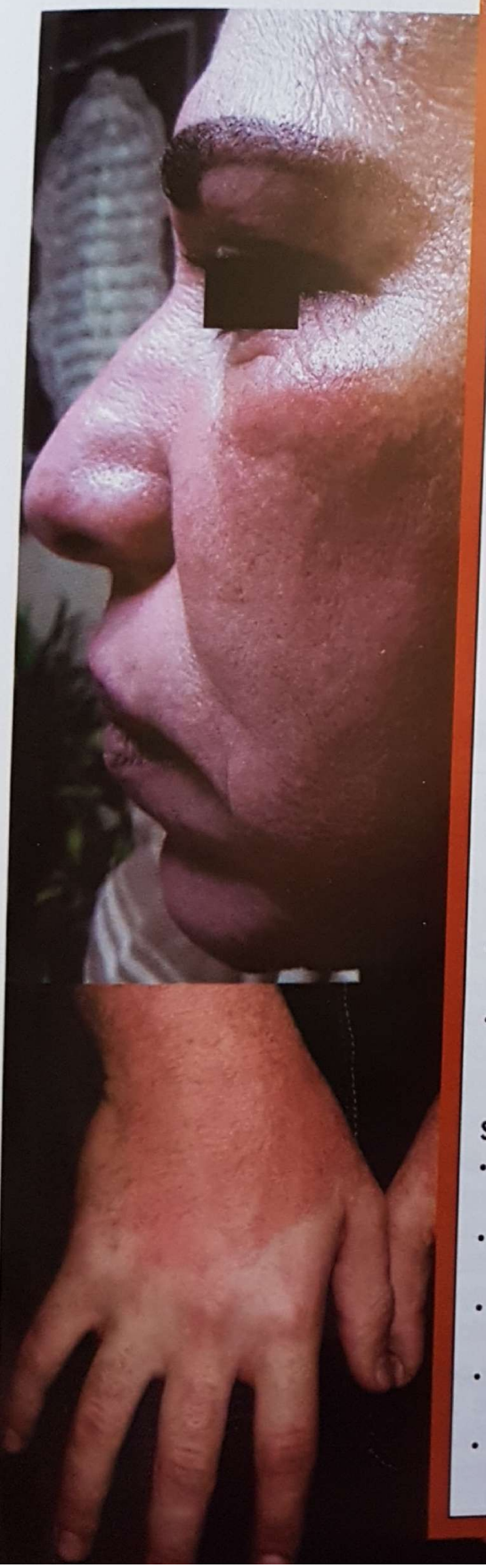
Photodermatoses ②



- Photodermatoses are skin disorders induced or exacerbated by light.
- **They can be broadly classified into four groups:** (i) Immunologically mediated photodermatoses (idioapathic), (ii) Drug- and chemical-induced photosensitivity, (iii) Defective DNA repair disorders, and (iv) Photoaggravated dermatoses.

Polymorphic light eruption

- The most common photodermatosis.
- Presents with papules, vesicles or plaques within hours of sun exposure; lasts for a few days.
- Action spectra: UVB, UVA, and, rarely, visible light.
- Management: Photoprotection, narrowband (NB)-UVB, PUVA, occasionally, brief courses of oral corticosteroids for acute attacks.

Actinic prurigo

- Severe form common in Native Americans (especially Mestizos), often with cheilitis and conjunctivitis.
- Childhood onset, often resolution by adolescence, but can persist indefinitely.
- Intensely pruritic, crusted papules or nodules in sun-exposed sites.
- Management: Photoprotection, NB-UVB, PUVA, thalidomide, topical calcineurin inhibitors.

Hydroa vacciniforme

- Very rare, childhood-onset photodermatosis.
- Papules and plaques develop umbilicated vesiculation, followed by hemorrhagic crusting (often severe) and varioliform scarring.
- Epstein-Barr viral infection has been detected in a number of patients.
- Management requires very careful photoprotection, including against UVA, and perhaps low-dose phototherapy to avoid provocation.

Solar urticaria

- A physical urticaria induced by sun exposure; lesions appear within 5 to 10 minutes and resolve over 1 to 2 hours.
- The action spectrum generally includes both UVA and visible light, but rarely UVB.
- There is a slight female predominance, with onset at any age.
- Estimated probability of resolution is 15% at 5 years, 25% at 10 years.
- Management: Photoprotection, high-dose, non-sedating antihistamines, low-dose UVA, PUVA, plasmapheresis & IVIg.

Photodermatoses* ②

Classification of photodermatoses

Immunologically mediated photodermatoses	Drug- & chemical-induced photosensitivity
• Polymorphous light eruption. • Chronic actinic dermatitis. • Actinic prurigo. • Hydroa vacciniforme. • Solar urticaria.	***Exogenous:*** • Phototoxicity: Systemic & topical. • Photoallergy: Systemic & topical. ***Endogenous:*** • Cutaneous porphyria.
Hereditary photodermatoses	**Photoaggravated dermatoses**
Caused by defects in nucleotide excision repair: • Xeroderma pigmentosum. • Cockayne syndrome, including cerebro-oculo-facio-skeletal syndrome. • Trichothiodystrophy. • Ultraviolet light sensitive syndrome. ***Caused by double strand break repair defects:*** • Rothmund-Thomson syndrome. • Bloom syndrome. ***Caused by abnormal chemical substances:*** • Smith-Lemli-Opitz syndrome. • Hartnup disease. ***Others:*** • Kindler syndrome.	• Atopic dermatitis. • Darier-White disease. • Dermatitis herpetiformis. • Herpes simplex infection. • Lupus erythematosus & neonatal lupus erythematosus. • Juvenile dermatomyositis. • Pellagra. • Psoriasis.

Laboratory evaluation of photosensitivity

- Routine histology.
- Antinuclear antibodies.
- Anti-Ro/SSA, -La/SSB antibodies.
- Plasma porphyrins, followed by complete porphyrin profile if positive.
- Phototesting to UVA, UVB and visible light.
- Photopatch testing.
- In infants and children, urinary amino acids.

Differential diagnosis of photodermatoses most commonly associated with different age groups**

When the patient is a child:
- Juvenile spring eruption.
- Childhood porphyrias (i.e. erythropoietic protoporphyria, congenital erythropoietic protoporphyria).
- Actinic prurigo.
- Hydroa vacciniforme.
- Genodermatoses.

When the patient is an adult:
- Polymorphous light eruption.
- Drug-induced photosensitivity.
- Solar urticaria.
- Lupus erythematosus.
- Porphyria cutanea tarda.

When the patient is old:
- Chronic actinic dermatitis.
- Drug-induced photosensitivity.
- Dermatomyositis.

* *Adapted mainly from:*
J Am Acad Dermatol, 2012; 67: 1093. e1-18.
J Am Acad Dermatol, 2012; 67: 1113.e1e15.
Bolognia et al., Textbook of Dermatology, Third edition, 2012.
** *Lim, et al., Wolverhampton, 2014.*

Phototesting*

Phototesting can confirm the presence of a photosensitivity disorder & is most helpful for the diagnosis of immunologically-mediated photodermatoses. Using an opaque template with several windows, the uninvolved skin of the back or the abdomen is exposed to varying doses of UVA, UVB &/or visible monochromatic or broad-spectrum radiation. Following light exposure, the first reading is performed in 20 minutes to detect urticarial lesions as seen in solar urticaria.

Photopatch testing*

Photopatch testing evaluates patients with photoallergic contact dermatitis. Photopatch testing is similar to a standard patch test used for evaluation of allergic contact dermatitis; a notable difference includes irradiation of the patch sites with UVA in the photopatch testing. Duplicate sets of photoallergen panels are placed on the back, & the sites are then covered with an opaque material to protect them from exposure to light. After 24 hrs, one of the panels is irradiated with a dose of 10 J/m^2 of UVA, or 50% of MED-A if the MED-A is significantly reduced. The other panel acts as the control.

Expected phototest & photopatch test results*

Disorder	MED for UVA	MED for UVB	Visible light	Photopatch test
Polymorphous light eruption	NL / ↓	NL / ↓	NL	Negative
Chronic actinic dermatitis	↓	↓	NL / ↓	Negative / positive
Solar urticaria	Urticaria	Urticaria	Urticaria	Negative
Phototoxicity	↓	NL	NL	Negative
Photoallergy	↓	NL	NL	Positive

NL: Normal

Polymorphous light eruption ❶

It is an abnormal reaction to sunlight (usually UVB, UVA & rarely, visible light from sunlight or other sources such as tanning beds).

Polymorphic light eruption is consistently the most common photodermatosis

It affects young adults, usually of light-complexion, mainly from May to October every year.

- **Clinically:** The eruption appears 4 hours to 4 days after sun exposure in the exposed areas, i.e. face, V-area of chest, neck, and arms. ***4 types are present:*** Papular, papulovesicular, diffuse erythematous and the plaque type (with scaly indurated plaque suggestive of DLE or lymphocytic infiltration of skin). There is no scarring or atrophy.

Juvenile spring eruption: Occasionally, the helices of the ears, particularly in boys because their ears are relatively more exposed, may be principally affected, often with vesicles. This form of PMLE sometimes referred to as "juvenile spring eruption".

NB: The tendency for the eruption to occur often diminishes or ceases as the summer or a sunny vacation proceeds, a phenomenon described as ***'hardening'.***

* *Lim et al., Photodermatology, 2014.*

- **Histopathology:** All types are non-specific except the plaque type: Patchy lymphocytic infiltrate resembling DLE, but the patchy infiltrate is perivascular (not periappendageal) & absent basal hydropic degeneration.
- **Diagnosis:** Positive phototesting with wave lengths below 320 nm (dose not rule-out LE). Negative lupus band test is more important.
- **Prophylaxis = Induction of hardening:**
  - Initiated during the spring.
  - 2-3 sessions weekly of NB-UVB or PUVA (about 5 weeks) + Oral prednisone (1 mg/kg) during the initial 7-10 days of the treatment to minimize photoexacerbation.
  - Patients are then asked to expose themselves to noonday sunlight for 15-20 minutes (without sunscreen) weekly for the remainder of the sunny season to maintain the hardened state.

  For NB-UVB: Initial starting dose is 50-70% the MED; the dose is then increased by 10-15% per treatment.

  For PUVA: 0.5-0.6 mg/kg of 8-methoxypsoralen is given 1 hour before UVA exposure; the starting UVA dose ranges from 0.5 to 3 J/cm^2, depending upon the skin phototype. The UVA dose is increased by 0.5 to 1.5 J/cm^2 per treatment.
- **Treatment:**
  - ***Topically:*** Steroids and sunscreens.
  - ***Systemic:*** Antihistamines (Periactin®), systemic steroids (in severe cases), antimalarials.

Actinic prurigo (Hutchinson's summer prurigo)

- **Onset:** Appears during childhood and is more frequently seen in girls. There is prurigo-like papules, small vesicles, and pitted scars present throughout the year but worst in summer involving exposed and covered areas. There is frequent personal or family history of atopy.
- **Management:** Photoprotection, NB-UVB, PUVA, thalidomide, topical calcineurin inhibitors.

Actinic prurigo vs PMLE

Feature	Actinic prurigo	PLME
Starts	2-9 years of age	9-29 years of age
Relation to UV exposure	Often noted later	Clear
Pruritus	Severe, persistent	Transient
Covered areas of body affected	Frequent	Rare
Scar formation		
Ears affected		
Distal one-third of nose affected		Never
Plaques on the philtrum		
Cheilitis of the lower lip		
Conjunctivitis	Possible	Never
HLA association	DR4/DRB1*0407	None
Prophylaxis	Difficult	Easy

Hydroa vacciniforme

- **Onset:** Early childhood. There is deep-seated umblicated vesicles on exposed areas. Healing occurs with large varioliform scars.
- Epstein-Barr viral infection has been detected in a number of patients.
- **Management**
  - Very careful photoprotection.
  - β-carotene, antimalarials, azathioprine, thalidomide, cyclosporine and dietary fish oil.

Chronic actinic dermatitis (CAD)

It seems that photosensitive eczema (PE), persistent light reactivity (PLR) and chronic photosensitivity dermatitis (PD) can be the precursors of actinic reticuloid (AR). The term chronic actinic dermatitis (CAD) has been proposed to consider this syndrome as a whole. The condition affects mainly elderly men over 50 years of age.

The diagnosis of CAD depends on:

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1. Persistent eczematous eruption of sun-exposed skin with possible extension into non-exposed areas.
2. Photosensitivity to UVB (<MED doses) and often also longer wave lengths.
3. Histologically, evidence of chronic eczema, with or without lymphoma like changes.

Pathogenesis: Transition from photoallergy to persistent light reactivity. Alteration in some normal skin component during the photoallergic reaction becomes antigenic on its own. If CAD supervenes, UVB irradiation may trigger the delayed-type hypersensitivity response at any site by formation of an antigenic photoproduct from the endogenous carrier protein alone or in the absence of exogenous initiating agents.

- Positive patch or photopatch tests common.
- **Management:** By photoprotection, avoidance of (photo) contact sensitizers, intermittent oral and topical corticosteroids, topical tacrolimus, low-dose PUVA, cyclosporine, azathioprine or mycophenolate mofetil.
- Probability of spontaneous resolution is 10% over 5 years, 20% over 10 years.

Actinic Reticuloid

- Severe and persistent photosensitivity with erythema, edema and striking "leonine" thickening of the light-exposed skin of the face, neck and hands.
- Patients with photosensitive atopic dermatitis are more likely to develop actinic reticuloid.
- The condition occurs almost exclusively in elderly men.
- There are lichenified plaques first in exposed areas, but later the eruption gradually spreads to cover most of the skin surface: → Erythroderma and generalized LN enlargement. There is ↑ thickening (deep furrows) & hyperpigmentation of the exposed areas. Itching is severe.

Leonine facies – associated dermatologic diseases

- Scleromyxedema.
- Systemic amyloidosis.
- Lipoid proteinosis.
- Lepromatous leprosy.
- Leishmaniasis.
- Cutaneous lymphoma (T-cell, B-cell).
- Actinic reticuloid form of chronic actinic dermatitis.
- Leukemia cutis.
- Mastocytosis (nodular).
- Sarcoidosis.
- Multicentric reticulohistiocytosis.
- Progressive nodular histiocytosis.
- Pachydermoperiostosis.

- The action spectrum is usually UVA, but shorter UVR (290-320 nm) may produce abnormalities.

Histopathology

- There is band like infiltrate of lymphoid and histiocytes in upper dermis and may extend into the lower dermis or invade into epidermis → aggregates resembling Pautrier microabscesses.
- In spite of its resemblance to MF or Sézary's syndrome, it is a benign & reversible. Also, T-cell in skin lesions & circulation are of the suppressor (OKT-8) type where in the CTCL it is of helper (OKT-4) type. There are several reports of lymphoma developing in patients with actinic reticuloid.

Treatment

- Systemic steroids.
- Azathioprine.
- PUVA.

Sunscreens are usually ineffective.

Solar Urticaria (SU)

- A physical urticaria induced by sun exposure; lesions appear within 5 to 10 minutes and resolve over 1 to 2 hours.
- It is characterized by immediate urticarial response to sunshine occurring in sun-exposed skin. Systemic symptoms may occur if there is sufficient mast cell release.
- The action spectrum generally includes both UVA and visible light, but rarely UVB.
- There is a slight female predominance, with onset at any age.

Classification of solar urticaria

	Mechanism	Action spectrum
Type I	Allergic	UVB
Type II	Unknown	UVA
Type III	Unknown	Visible light
Type IV	Allergic	Visible light
Type V	Unknown	UVA, UVB, visible light
Type VI	Protoporphyrin	Visible light

Type VI is considered erythropoeitic protoporphyria.

Pathogenesis: *A chromophore (precursor) present in the skin or in the circulation, or both may absorb radiation → photoallergen formation. IgE-mediated hypersensitivity to this photoallergen then develops with mast cell activation.*

Treatment

- *Avoidance and sunscreens.*
- *High-dose, non-sedating antihistamines.*
- *PUVA: It may cause depletion of mast cell contents.*
- *Plasmapheresis, and IVIg.*

Solar (actinic) elastosis

It occurs after prolonged exposure to sun rays especially in fair-skinned persons. Small yellowish papules and plaques develop on face and backs of the bands. The skin shows deep furrows and wrinkles and subject to development of actinic keratoses and carcinomas.

Cutis rhomboidalis nuchae: The skin on the back of the neck becomes thickened and tanned with exaggerated normal skin markings.

Histopathology

- ***Hx & E:*** In upper dermis, there is basophilic degeneration of the collagen separated from the atrophic epidermis by a narrow band of normal collagen.
- ***By Elastic tissue stain:*** There are aggregates of thick, interwoven bands of elastotic material which is newly formed by fibroblasts which are no longer capable of producing normal elastic fibers or collagen.

Nodular elastosis with cysts & comedones (Favre-Racouchot syndrome)

Some patients with pronounced solar elastosis of the facial skin show especially lateral to the eyes, multiple comedones as well as yellowish nodules and contain a central comedo.

A variant of nodular elastosis with cysts and comedones is the ***actinic comedonal plaque.*** It is found as a solitary plaque on sun-damaged skin of either the arms or the face. The plaque shows small nodules and dilated follicles.

Histopathology: Pronounced solar elastosis, dilated pilosebaceous openings and large, round cysts that are lined by a flattened epidermis and represent greatly extended hair follicles.

Photosensitivity

A number of substances known as photosensitizers may induce an abnormal reaction in skin exposed to sunlight. These photosensitizers come in contact with the skin through external or internal routes (Figs 1-3).

Fig. 1. Photosensitivity

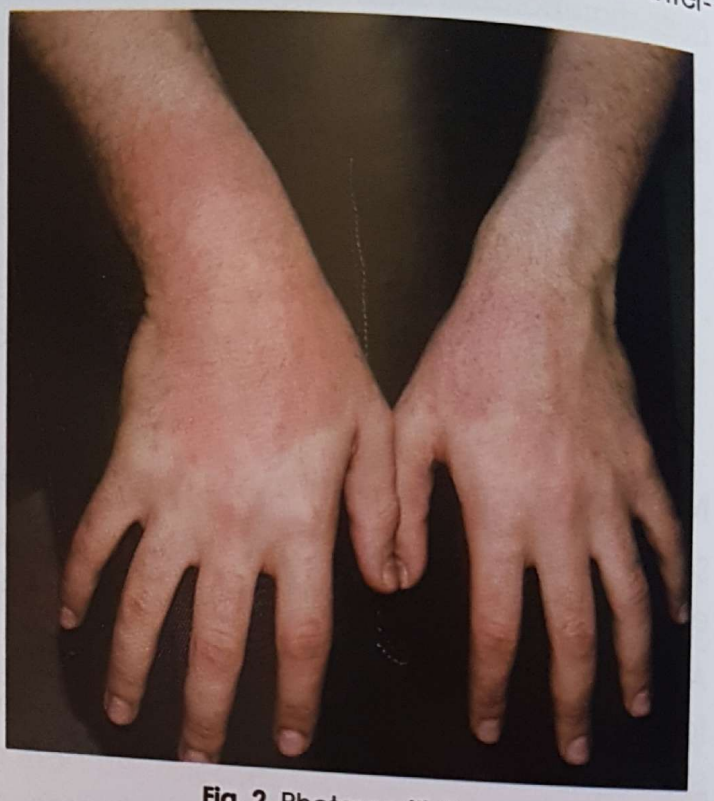

Fig. 2. Photosensitivity

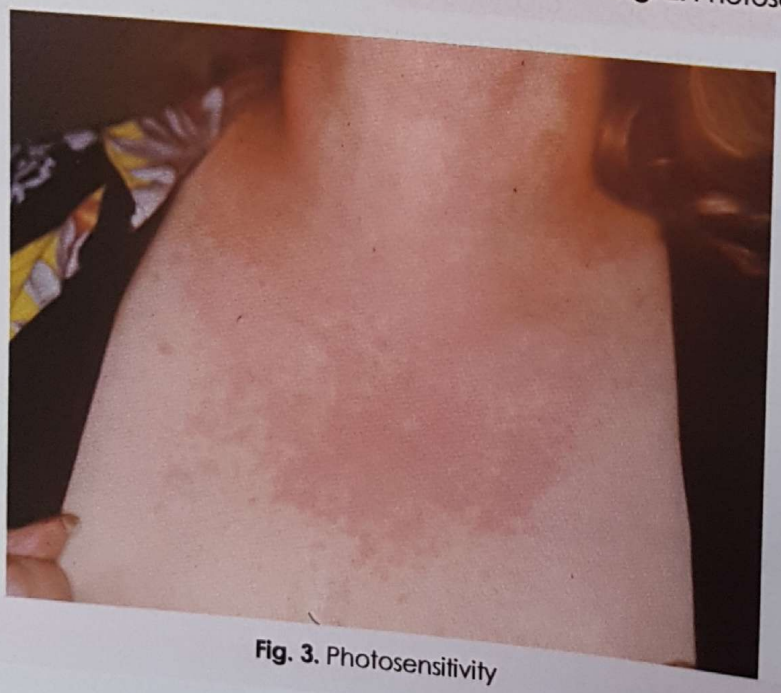

Fig. 3. Photosensitivity

I) Phototoxic reactions

- Phototoxicity is characterized by an exaggerated sunburn-like reaction (Figs 4, 5), usually caused by systemic agents. The cutaneous porphyrias are an example of phototoxicity induced by endogenous agents.
- It is a non-immunologic reaction that can be elicited in the majority of individuals 2-6 hrs after exposure of the photosensitizers, if given in sufficient dose and in association with exposure to light of proper wave length (usually 280-450 nm).

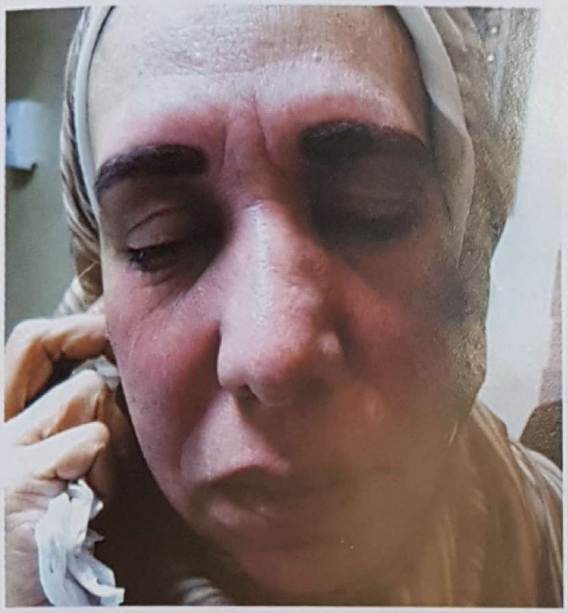

Fig. 4. Phototoxic reaction

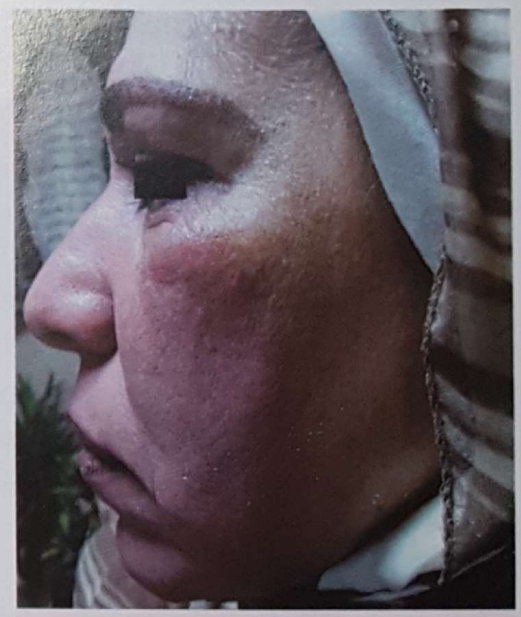

Fig. 5. Phototoxic reaction

- **The cytotoxic effects are due to generation of:**
  - O_2 free radicals, superoxide anions, hydroxyl radicals and singlet oxygen.
  - Stable photoproducts (reported with chlorpromazine and tetracyclines).
  - Photoadducts (reported with psoralens).
  - Inflammatory mediators (reported with porphyrins).
- **Phototoxic drug reactions:** Manifested as severe sunburn without itching, e.g. with sulfonamides, doxycycline, and psoralens,
- **Phototoxic contact dermatitis:** As with coal tar derivatives and psoralens as oil of bergamot which are present in some perfumes → **Berloque or perfume dermatitis** (Fig. 6), which is manifested as streaking or drop-shaped lesions on sides of neck.

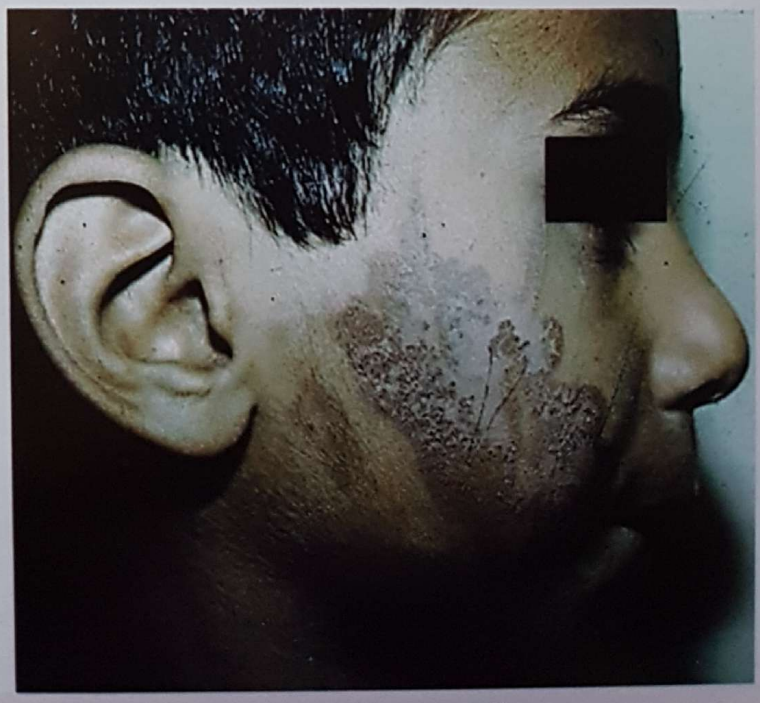

Fig. 6. Berloque dermatitis

II) Photoallergic reactions

- Photoallergy presents with eczematous lesions, most commonly related to topical photoallergens.
- It is a cell mediated, delayed immunologic response that can be elicited only in small number of individuals who have been sensitized by previous exposure to photosensitizer drugs and at the same time to light as in allergic contact dermatitis.
- The role of light consists in altering either the hapten itself or the avidity with which the hapten combines with the carrier protein to form a complete photoantigen.
- A photoallergic drug eruption causes a photocontact dermatitis in all light-exposed areas. Like any allergic contact dermatitis, it causes itching.
- ***Photoallergic drug reactions:*** e.g. chlorothiazides, tolbutamide (oral antidiabetic), phenothiazines (chlorpromazines).
- ***Photoallergic contact dermatitis:*** e.g. sulfathiazides and antihistamine.

Histopathology

- ***Phototoxicity:*** Characterized by scattered necrotic keratinocytes ('sunburn cells') & a dermal infiltrate of primarily lymphocytes and neutrophils.
- ***Photoallergy:*** Characterized by epidermal spongiosis plus a dermal lymphohistiocytic infiltrate, indistinguishable from other causes of spongiotic dermatitis.

Treatment of photosensitivity (Fig. 7)

- Identification and avoidance of the offending agent. If this is not possible, strict photoprotection (UVB and UVA) is required.
- For phototoxic reactions, analgesia may be helpful. Topical corticosteroids, and, for severe flares, short courses of systemic corticosteroids, can be used for photoallergic dermatitis. Occasionally, evening dosing of a phototoxic drug can be done so that peak systemic levels occur during the night.

Fig. 7. Photosensitivity & physical urticaria (a & b) before treatment, (c & d) after treatment with sunscreen & antihistamines

Phytophotodermatitis

- It is a form of phototoxicity caused by the combination of a topical or oral photosensitizing agent (furocoumarins "psoralens and angelicins" are the most common agents) followed by exposure to the appropriate wavelength of UV radiation. Limes, celery and rue are the most common causes.
- Because this is not an immunologic reaction, no prior sensitization is necessary and anybody can be affected.
- Photoallergic reaction to a plant is exceedingly rare.

Clinical features

- Cutaneous sensitivity to UV light peaks 30-120 minutes after contact with furocoumarins.
- Bizarre configurations of erythema, edema & bullae appear after 24 hours & peak at 72 hours.
- These painful, non-pruritic reactions are more often seen in mid to late summer, when psoralen concentrations are highest in the offending plants and more skin is exposed to direct sunlight.
- Hyperpigmentation appears 1-2 weeks later and lasts months to years.
- Occasionally, low-dose UVA and/or psoralens cause hyperpigmentation without a preceding vesicular or erythematous eruption.

Treatment

- Prevent contact with the offending plants.
- If contact occurred → prompt washing with soap and water may prevent a reaction.

The differential diagnosis of photodermatoses most commonly associated with lesion morphology*

Morphology	Possible diagnosis
Urticaria or urticarial	• Solar urticaria • Erythropoietic protoporphyria
Papule	• Polymorphous light eruption • Actinic prurigo • Chronic actinic dermatitis
Vesicle	• Polymorphous light eruption • Juvenile spring eruption • Porphyria cutanea tarda • Variegate porphyria • Coproporphyria • Phototoxicity • Photoallergy • Hydroa vacciniforme
Erosion, crust	• Actinic prurigo • Hydroa vacciniforme • Porphyrias (PCT, VP, CEP, HC)
Eczema &/or lichenification	• Chronic actinic dermatitis
Erythema	• Phototoxicity
Scars	• Hydroa vaccinforme • PCT • VP • CEP

CEP: Congenital erythropoietic porphyria, HC: Hereditary coproporphyria, PCT: Porphyria cutanea tarda, VP: Variegate porphyria.

Classification & action spectra of photosensitive skin diseases

Disease	Spectrum of light		
	UVB	UVA	Visible
Polymorphic light eruption	+	++	
Hydroa vacciniforme	+	++	
Solar urticaria	+	++	++
Chronic actinic dermatitis	+++	++	+
Actinic prurigo	++	++	
Photoallergic contact dermatitis		+++	
Photoirritant contact dermatitis		+++	
Photodrug reactions	+	+++	+
Porphyria		++	+++
Cutaneous lupus erythematosus	+++		

* *Lim, et al., Wolverhampton, 2014.*

- ***Iron oxide*** offers protection across the UV spectrum and into the visible range, and is used as a colorant in some products.
- ***Other "active" ingredients*** have been added to sunscreens, with claims of increasing efficacy of the finished products, e.g. Antioxidants, including vitamins E, C & green tea polyphenols.
- ***Boosters:*** They are not UV filters, but they serve to increase the protective nature of sunscreens. Examples include tiny spheres that scatter incoming radiation and agents that increase the spread of the sunscreen on the skin, leading to greater protection.

Efficacy of the sunscreen

Depends on the vehicle, pH stability, SPF, the type of the skin (color and thickness), environment, sweating, substantivity (the sunscreen remains effective after prolonged sweating or swimming).

Determination of the sun protection factor (SPF)

- **Instrumentation:** Light source which mimics solar spectrum.
- **Procedure:** Determine minimal erythema dose (MED) in protected* & unprotected skin.
- **SPF =** $\frac{\text{MED protected}}{\text{MED unprotected}}$
- **To test substantivity** – after application & before MED testing:
  - Water resistant (40): 2 x 20 min water immersions (whirlpool bath)†.
  - Water resistant (80): 4 x 20 min water immersions (whirlpool bath)†.

** Sunscreen product applied at 2 mg/cm².*
† Air drying in between immersions.

- A product with an SPF of 10 would allow 10 times as much time in the sun with the same resultant level of erythema as without the product in a given individual.
- An SPF 20 similarly would allow 20 times as much exposure with the same result, but this does not mean that the SPF 20 product absorbs twice as much radiation as the SPF 10 product.

Labeling of sunscreens – ultraviolet B (UVB) and ultraviolet A (UVA) protection (2011)

Ultraviolet B (UVB) protection
• Sun protection factor (SPF): Up to 50+
Ultraviolet A (UVA) protection
• Either no label or broad spectrum. • Broad spectrum can be used if critical wavelength is ≥ 370 nm.
Substantivity
• Water resistant (40 minutes) or water resistant (80 minutes). • No use of the following designations: "Waterproof", "sunblock", "all day protection", or "sweat proof".
Additional labeling
• If a sunscreen has SPF ≥15 and is broad spectrum, then can state that the product can help to reduce the risk of skin cancer & the risk of early skin aging, when used regularly & as directed in combination with other sun protection measures. • If the SPF of the sunscreen is <15 or it is not broad spectrum, then it must have the following skin cancer/skin aging alert: "Spending time in the sun increases your risk of skin cancer & early skin aging. This product has been shown only to help prevent sunburn, not skin cancer or early skin aging".

Sun protection is advised to:

- Fair-skin (skin types 1 & 2).
- Sun-sensitivity disorders.
- Personal or family history of skin cancer.
- Outdoor occupations.

Adverse effects of sunscreens are:

- Minor skin irritation, which is common.
- Allergic contact dermatitis, which is rare.
- Effect on Vitamin D:
  - Sunscreens that are effective at blocking UVB photons may block some cutaneous vitamin D synthesis.
  - A diet that includes vitamin D rich foods and moderate amounts of supplements combined with a modest amount of everyday sun exposure is enough to maintain adequate serum vitamin D levels, even if the individual photoprotects with sunscreen.

II) Systemic photoprotection

e.g. beta-carotenes & antimalarials *(see also chapter 18, page 95)*.